DEPARTMENT OF HEALTH & HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Public Health Service

Memorandum

Date AUG - 7 1999

1987 '99 AUG 11 P2:12

From Senior Regulatory Scientist, Regulatory Branch, Division of Programs & Enforcement Policy (DPEP), Office of Special Nutritionals, HFS-456

Subject 75-day Premarket Notification for New Dietary Ingredient

To Dockets Management Branch, HFA-305

New Dietary Ingredient:	*Haematococcus pluvialis* algae
Firm:	Cyanotech Corporation
Date Received by FDA:	May 25, 1999
90-day Date:	August 23, 1999

In accordance with the requirements of section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act, the attached 75-day premarket notification for the aforementioned new dietary ingredient should be placed on public display in docket number 95S-0316 after August 23, 1999.

Robert J. Moore, Ph.D.

95S-0316

RPT 50

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington, DC 20204

AUG - 7 1999

R. Todd Lorenz, Ph.D.
Scientific Director
Cyanotech Corporation
73-4460 Queen Kaahumanu Highway
#102
Kailua-Kona, Hawaii 96740

Dear Dr. Lorenz:

This is to notify you that your submission pursuant to section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (the Act) dated May 20, 1999, concerning the marketing of a substance that you assert is a new dietary ingredient (i.e., *Haematococcus pluvialis* algae) was received by the Food and Drug Administration (FDA) on May 25, 1999. Your submission will be kept confidential for 90 days from the date of receipt, and after August 23, 1999, your submission will be placed on public display at Dockets Management Branch (Docket No. 95S-0316). Commercial and confidential information in the notification will not be made available to the public.

Please contact us if you have questions concerning this matter.

Sincerely,

Robert J. Moore, Ph.D.
Senior Regulatory Scientist
Division of Programs and Enforcement Policy
Office of Special Nutritionals

CYANOTECH CORPORATION

ISO 9002-94 CERTIFIED
QUALITY MANAGEMENT SYSTEM

Thursday, May 20, 1999

Robert Moore
Division of Programs and Enforcement Policy
Office of Special Nutritionals
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C Street SW
Washington DC 20204

RE: New Dietary Ingredient Notification for *Haematococcus* algae

Dear Dr. Moore,

We received your letter stamped April 28, 1999 with concern about the New Dietary Notification for *Haematococcus* algae. We have included the references pertaining to "A Technical Review of *Haematococcus* algae" as requested. Safety studies with *Haematococcus* algae were sent in the previous package. We include two more studies entitled "*Haematococcus pluvialis*, unicellular algae 14-day Oral Toxicity Study in Rats" and "*Haematococcus pluvialis*, unicellular algae Acute Toxicity Study in Rats Treated by Oral Route" (Appendix 6 and 7, respectively).

Astaxanthin and other carotenoids produced by *Haematococcus* algae have a long history of use in the human diet, occurring naturally in salmonid fish, shrimp and lobster. A recent study was conducted to assess the astaxanthin concentration and isomeric composition in a large variety of wild salmonid species. This survey showed a range of astaxanthin concentrations in the flesh of these fish from 1-58mg/kg (Appendix 1, Turujman et al., 1997). I have summarized the results in Table1 and calculated the average concentrations of each species and as an average of all species combined.

TABLE 1

Species	astaxanthin range	astaxanthin average
Wild sockeye salmon	30-58 mg/kg	40.4 mg/kg
Wild Coho salmon	9-28 mg/kg	13.8 mg/kg
Wild pink salmon	3-7 mg/kg	5.4 mg/kg
Wild chum salmon:	1-8 mg/kg	5.6 mg/kg
Wild Chinook king salmon	1-22 mg/kg	8.9 mg/kg
Wild Atlantic salmon	5-7 mg/kg	5.3 mg/kg

avg. all species=13.2 mg/kg

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It can be seen from the table that the average astaxanthin concentration ranges from a low of 5.3 mg/kg in Atlantic salmon to 40.4 mg/kg in sockeye salmon. The average of all species was calculated to be 13.2 mg/kg. Since the average human would consume about 0.25 kg of fish flesh in one meal, this results in the lowest intake of 1.325 mg of astaxanthin from Atlantic salmon, 3.3 mg of astaxanthin from the "all species average" fish and 10.1 mg of astaxanthin from sockeye salmon. We propose a daily consumption of only 2 mg/day of astaxanthin from *Haematococcus* algae. Even at 5 times the recommended dosage (10 mg), this would be equivalent to consuming about 0.25 kg of sockeye salmon.

Canthaxanthin, lutein and beta-carotene are less than 5% the level of astaxanthin in *Haematococcus* algae, seen in the attached chromatograms (Appendix 2). These carotenoids are commonly found in fruits and vegetables of the normal human diet. Canthaxanthin, lutein and beta-carotene intake from *Haematococcus* algae meal would be less than 0.1 mg/day. Canthaxanthin is currently allowed for use in coloring foods under CFR 21 section 73.75 at levels not to exceed 30 mg/ pound of food or pint of liquid food. Thus, the canthaxanthin and other carotenoids ingested from the recommended dose of *Haematococcus* algae is 300-fold less than a pound of food or pint of liquid colored with canthaxanthin.

We are aware that very high doses of canthaxanthin have been used in the past as an artificial tanning agent. These supplements under various trade names (Orobronze, Darker Tan, BronzeGlo and Carotenoid-N, which consists of 35 mg of canthaxanthin and 25 mg of beta-carotene (R. Bluhm et al. 1990. JAMA. 264:1141-1142.). Consumers may have taken 2-3 of these supplements daily and this was eventually found to be associated with asymptomatic crystalline retinopathy. Another paper studied 51 individuals that ingested from 3.6 to 66 grams of canthaxanthin within a 24 month period. Six of 51 had deposits in the ocular fundus that appeared to be related to the ingestion, but no functional impairment could be detected (Boudreault et al. 1983. Can J. Opthalmol. 18:325-328). Another supplement called Phenoro contained 15 mg canthaxanthin and 10 mg beta-carotene and was used at 4-8 doses/day amounting to 7,200-25,200 mg of canthaxanthin annually. One study examined 53 patients that had taken from 7,500-178,000 mg of canthaxanthin and found just 41% had gold colored deposits on their retinas but all had normal vision and no subjective complaints. Another study cited was 12% of people who ingested from 3,500-60,000 mg canthaxanthin had crystalline deposits, but with no subjective complaints nor functional defects. Beta-carotene, for that matter, does not accumulate in the retina (Ros et al. 1985. Photodermatol. 2:183-185). These "megadoses" of canthaxanthin would not be a concern with *Haematococcus* algae as the canthaxanthin concentration is relatively very low. Other carotenoids such a lutein and beat-carotene are also of small percentage and normal carotenoids of the human vegetable and fruit diet. The annual dosage of astaxanthin from *Haematococcus* algae meal would be only 2 mg per day or 730 mg/year.

On page 11 of Appendix 4, it is noted that unlike canthaxanthin, astaxanthin does not form crystals in the retina and does not otherwise adversely affect the eye.

Astaxanthin is approved for use in salmonid feeds under 21 CFR section 73.35 at a maximum level of 80 mg/kg. This petition was reviewed by the FDA as CAP 7C0211 and included numerous safety studies with astaxanthin. Volume 2-6 of this petition contains the summaries and complete reports from the studies. The acute toxicity of 10 consecutive daily oral doses astaxanthin in rats was found to be greater than 2000 mg/kg. There was no mortality or symptoms of toxicity reported. In the Ames mutagenicity test, astaxanthin concentrations ranging from 0.03-5.0 mg/plate did not induce mutations in *Salmonella typhimurium* tester strains with or without activation by rat liver homogenate. Astaxanthin administered to mice at 500, 1000, and 2000 mg/kg did not induce chromosome breaks or mitotic disjunction. In teratology and embryotoxicity studies with rabbits, doses ranging from 100-400 mg/kg/day were administered to pregnant animals. There were neither overt signs of maternal sensitivity to the treatment nor significant changes in body weight development or malformations among the fetuses compared to the controls. Other safety studies included reproductive performance in rats with P and F1 generations, 13-week tolerance study in rats, and 13-week tolerance study in dogs all without toxic effects. The full volume of these safety studies are available in CAP 7C0211 at the FDA, I have included the summary for brevity (Appendix 3).

US patent 5,527,533 (Appendix 4, Tso et al. 1996), claims a method of retarding and ameliorating eye diseases and injuries by administering astaxanthin in a therapeutically-effective dose. Within this patent a preferable amount of 10-200 mg/kg of body weight per dose is claimed to retard a degenerative disease of the central nervous system or the eye, or to ameliorate damage resulting from an injury or a disease of the central nervous system or eye. This is equivalent to 682-13,636 mg dosage for a 150 lb person. On page 11 of Appendix 4, it is noted that unlike canthaxanthin, astaxanthin does not form crystals in the retina and does not otherwise adversely affect the eye. Again, we exemplify that 2 mg of astaxanthin per day from *Haematococcus* algae is a relatively low amount that would normally be consumed in the human diet from salmonids or shrimp.

It has been recommended that mixed natural carotenoids be used as supplements The usual doses of carotenoids are 20-60 mg (33,000-100,000 IU) per day for beta-carotene, 10-30 mg of alpha-carotene, and 3-6 mg each of lutein, lycopene and zeaxanthin (Appendix 5). Astaxanthin does have a long history of use in the human food chain and has been marketed in the US and Europe in different forms. Itano Refrigerated Food Co. Ltd. (Tokushima, Japan) markets astaxanthin from extracted Antarctic krill as a human supplement. This product is distributed by the U.S. company OptiPure as "Astax-1700" as seen from their webpage at www.optipure.com/plist.htm. AstaCarotene (Sweden) produces and markets *Haematococcus* algae as "Astaxin" for distribution in Europe recommending 4 mg/day of astaxanthin. Acadiana Processors (Palmetto, LA) also produces an astaxanthin extract from crustaceans, which is sold in the US.

CYANOTECH CORPORATION

We contend that we have supplied reasonable assurance that *Haematococcus* algae, when used as recommended, does not present a significant or unreasonable risk of illness or injury and ask you to reconsider your ruling. Thank you for your attention to this matter. If you have any questions please do not hesitate to contact me at 808-326-1353 (ext. 115).

Kind regards,

R. Todd Lorenz, Ph.D.
Scientific Director

CC: Dr. Gerry Cysewski, CEO Cyanotech Corporation